

REMARKS

Claims 1, 3-15 and 30-32 are currently pending in this application. In this response, previously pending Claims 2 and 22 are cancelled without prejudice and Claims 1, 3, and 9 are currently amended. New Claims 30, 31, and 32 are presented in this response.

Support for Claim Amendments

The preceding claim amendments are supported within the text of the Application as originally filed as follows.

Claim 1 For “(a) washing and cooling insulin responsive cells in ice cold buffer,
(b) incubating said insulin responsive cells from (a) in the presence of insulin,”
see at least Page 19, lines 32-35. (“The premise of the basic *in vitro* assay is diagrammed in Fig. 1A. Fully differentiated 3T3-L1 adipocytes in the basal state were first cooled rapidly by washing with ice-cold buffer, and then maintained at 4⁰C in the presence or absence of 1 μM insulin.”)

For “a membrane fraction, which comprises a membrane ~~fraction~~ fraction, which comprises (i) an insulin receptor, (ii) an IRS-1 (“insulin receptor substrate -1”), (iii) an IRS-2 (“insulin receptor substrate -2”), (iv) a p85 subunit of PI-3 Kinase (“phosphatidyl-inositol 3-kinase”)” see at least page 20, lines 14-22. (“The insulin receptor was highly enriched in the PM fraction and the amount did not vary with exposure to insulin. IRS-1 and IRS-2 were found mainly in the LDM and, to a lesser extent, the CYT fraction as previously reported (Inoue, 1998)” and “The p85 subunit of PI 3-kinase was present to a significant degree in all three subcellular fractions.”).

For “a cytoplasmic fraction, which comprises PDK1 (“phosphoinositide-dependent kinase 1”) activity, an IRS-1 (“insulin receptor substrate -1”), an IRS-2

Support for Claim Amendments (continued)

(“insulin receptor substrate -2”), a p85 subunit of PI-3 Kinase (“phosphatidylinositol 3-kinase”) see at least page 20, lines 14-22 as cited above.

Claim 1 For “(e) incubating said assay mixture at about 37°C for up to about 15 minutes;” see at least Page 20, lines 9-10 (“and incubated at 37 °C for up to 15 minutes”).

Claim 1 For “wherein following step (e) said insulin receptor is autophosphorylated, said IRS-1 and said IRS-2 are phosphorylated, said p85 subunit of PI 3-kinase is bound to said IRS-1 and to said IRS-2, a PI 3-kinase is activated, said PDK1 is activated, said PDK2 is activated,” see at least Page 22, lines 3-7 (“The time course for insulin receptor-mediated tyrosine phosphorylation under the optimal conditions described above was followed by immunoblot analysis using an anti-phosphotyrosine antibody. Two bands at ~160 kDa and ~95 kDa appeared in response to insulin, corresponding to the molecular mass of IRS-1/2 and the β subunit of the insulin receptor, respectively (Fig. 3A).”). Also see at least Page 22, lines 16-20 (“After solubilizing the reaction mixture with 1% Triton X-100, tyrosine-phosphorylated proteins capable of co-immunoprecipitating with the p85 subunit of PI-3 kinase were detected by immunoblot analysis (Fig. 3B, bottom panel). Insulin stimulated the association of PI-3 kinase with a tyrosine-phosphorylated protein doublet corresponding to the molecular mass of IRS-1 and IRS-2, mimicking what occurs *in vivo*...”). Also see at least Page 24, lines 14-17 (“Thus, the PI 3-kinase-dependent Akt activation in our *in vitro* system is likely to reflect the preservation of signaling compartmentalization that takes place *in vivo* at the interface between the membrane lipid bilayer and the aqueous phase.”). Also see at least Page 26, lines 27-30 (“In an *in vitro* reaction combining immunodepleted CYT with PM, the lack of PDK1 resulted in greatly diminished

insulin-stimulated phosphorylation of Akt on Thr308, as expected; however, insulin-stimulated Ser473 phosphorylation occurred normally (Fig. 7B, left panels)"). Also see at least Page 29, lines 28-31 ("Adding the extracted proteins back to the salt-washed PM and CYT recovered the stimulated-PDK2 activity with no effect on Thr308 phosphorylation. Thus, the data suggested that PDK2 could be dissociated from the bulk plasma membrane fraction by salt extraction in functional form.

Claim 9 For "a cytoplasmic fraction, which comprises a protein kinase B and a PDK1 ("phosphoinositide-dependent kinase 1") activity," see at least Page 20, line 22 ("PDK1 was mainly found in the cytosol").

For "producing a desalted aqueous fraction comprising less than 145 mM chloride and a PDK2 ("phosphoinositide-dependent kinase 2") activity," see at least Page 29, lines 23-25 ("Adding the desalted protein extract (Ext-LoS) back to the reaction containing the salt-washed PM and the cytosol recovered the PDK2 activity but had no effect on the PDK1 activity.")

Claim 30.(New) For "wherein said insulin responsive cells are incubated in ice cold buffer in step (b)" see at least Page 19, lines 32-35. ("Fully differentiated 3T3-L1 adipocytes in the basal state were first cooled rapidly by washing with ice-cold buffer, and then maintained at 4°C in the presence or absence of 1µM insulin.")

Claim 31.(New) For "comprising the step of adding a phosphatidylinositol phosphate compound to the assay mixture in step (d)" see at least Page 27, lines 10-25.

Claim 32.(New) For the "method of Claim 31 wherein said insulin responsive cells are incubated in the absence of insulin in step (b)" see at least Page 19, lines 32-35 as shown above for claim 30.

Specification:

In the Action, the Examiner alleged that page 30 of the specification is missing. It now appears that page 30 was not included in the application as originally filed. Applicant has amended the specification to delete the sentence fragments of previously filed pages 29 and 31.

Claim Objections:

Examiner objected to Claim 22 as a duplicate of Claim 5. Applicant has addressed this objection by canceling Claim 22.

35 U.S.C. § 102(b):

Claims 1-4, 7 and 8 stand rejected for allegedly lacking novelty in light of Wijkander et al. (Journal of Biological Chemistry, 1997, 272(34):21520-21526), Alessi et al. (Current Biology, 1997, 7:261-269) and Cross et al. (Nature, 1995, 378:785-789). The Examiner alleged that Wijkander teaches cytosol fractions and membrane fractions of rat adipocytes, which were combined in a buffer that lacked chloride ions. A PKB assay was performed by addition of ATP and 40 mM MgCl₂. Alessi allegedly discloses that full activation of PKB requires phosphorylation of Ser473 and Thr308. Cross allegedly discloses that PKB phosphorylates GSK3.

Applicant respectfully asserts that the claimed invention is novel. As specifically noted in the specification (see Page 23, lines 5-7), a key aspect of the claimed invention is that it activates protein kinase B by reconstituting the entire early insulin signaling pathway from binding of insulin to its receptor through to phosphorylation of GSK3 ("glucose synthase kinase-3") by the activated protein kinase B. More specifically, the present invention successfully reconstitutes in vitro the 1) autophosphorylation of the insulin receptor (pp. 1 and 26 of the specification); 2) recruitment of IRS ½ to the plasma membrane and tyrosine phosphorylation of these adapter molecules (pp. 1 and 22); 3) activation of PI 3 kinase after binding to IRS ½ (pp. 23 and 24, Figure 5C); 4) activation of PDK1 as observed by the phosphorylation of threonine on PKB (p. 26); and 5) activation of PDK2 as observed by the phosphorylation of serine on PKB (p. 29). The method Claim 1 as currently amended now reflects the key steps permitting activation

of protein kinase B by reconstitution of the early insulin signaling pathway. For example, Claim 1 now recites the steps of: “(a) washing and cooling insulin responsive cells in ice cold buffer”, “(b) incubating said insulin responsive cells from (a) in the presence of insulin,” and “(e) incubating said assay mixture at about 37°C for up to about 15 minutes”. Claim 1 also now recites the events permitting activation of protein kinase B by reconstitution of the early insulin signaling pathway. For example, Claim 1 now recites:” wherein following step (e) said insulin receptor is autophosphorylated, said IRS-1 and said IRS-2 are phosphorylated, said p85 subunit of PI 3-kinase is bound to said IRS-1 and to said IRS-2, a PI 3-kinase is activated, said PDK1 is activated, said PDK2 is activated, and said protein kinase B is activated in the assay mixture”.

In contrast to the instant invention, the Wijkander et al. reference does not anticipate nor suggest an *in vitro* method for activating protein kinase B wherein the insulin receptor is autophosphorylated, IRS-1 and IRS-2 are phosphorylated, the p85 subunit of PI 3-kinase is bound to IRS-1/-2, and PI 3-kinase, PDK1, and PDK2 are activated as currently specified by the claims. The Wijkander et al. reference merely demonstrates only that one can obtain from insulin-treated cells a protein kinase B that has been activated *in vivo*. Activation of protein kinase B *in vitro*, as taught in the instant invention, permits various studies of the protein kinase B activation process that cannot be performed in the *in vivo* system disclosed in Wijkander such as immunodepletion of cellular factors or addition of membrane impermeable reagents (see Page 23 of specification). The deficiencies of the Wijkander et al. reference with respect to anticipating the claimed method for activating protein kinase B *in vitro* by reconstituting the early insulin signaling pathway are not remedied by the Alessi et al. reference, which simply discloses that full activation of protein kinase B requires phosphorylation of Ser473 and Thr308. The Cross et al. reference simply discloses that protein kinase B phosphorylates GSK3 and also thus fails to remedy the deficiencies of the Wijkander et al. reference with respect to anticipation or suggestion of the currently claimed *in vitro* method for activating protein kinase B by reconstituting the early insulin signaling pathway.

Furthermore, to anticipate a claimed invention and support a rejection under 35USC§102, a single reference must teach each and every element of the claimed invention.

MPEP 2131.01 states:

“Normally, only one reference should be used in making a rejection under 35 U.S.C. §102. However, a 35 U.S.C. §102 rejection over multiple references has been held to be proper when the extra references are cited to: (a) Prove the primary reference contains an "enabled disclosure;" (b) Explain the meaning of a term used in the primary reference; or (c) Show that a characteristic not disclosed in the reference is inherent.”

In this instance, it appears that the Examiner combines the Cross et al. and Alessi et al. references with the Wijkander et al. reference in order to furnish claim elements such as phosphorylation of GSK3 and phosphorylation of serine and threonine residues of protein kinase B that are lacking in the Wijkander et al. reference. The Cross et al. and Alessi et al. references are not being used by the Examiner to prove that the Wijkander et al. reference contains an enabled disclosure, to explain a term in the Wijkander et al. reference, or to show that a characteristic not disclosed in the Wijkander et al. reference is inherent. Consequently, it is not proper to combine the Cross et al. and Alessi et al. references with the Wijkander et al. reference to provide claim elements absent from the Wijkander et al. reference in support of a 35 U.S.C. §102 rejection.

Given that the Wijkander et al., Cross et al. and Alessi et al. references fail to anticipate the claims as currently amended either in isolation or in aggregate, applicant submits that the Examiner's rejections of Claims 1-4, 7, and 8 under 35 U.S.C. §102b have been overcome. Applicant therefore respectfully requests withdrawal of the rejections of Claims 1-4, 7, and 8 under 35 U.S.C. §102b.

35 U.S.C. § 103:

Claims 1-4, 7, and 8 stand rejected as allegedly obvious in light of the combined teachings of Wijkander, Alessi and Cross.

Applicant reasserts its arguments above with respect to the failure of the Wijkander et al. reference in combination with Alessi et al. and Cross et al. to anticipate each and every element of the claims as currently amended. More specifically, the combination of the Wijkander et al.,

Alessi et al. and Cross et al. references does not teach an *in vitro* method for activating protein kinase B wherein the insulin receptor is autophosphorylated, IRS-1 and IRS-2 are phosphorylated, the p85 subunit of PI 3-kinase is bound to IRS-1/-2, and PI 3-kinase, PDK1, and PDK2 are activated as now specified in the currently amended claims. Whereas the Wijkander et al. reference merely demonstrates only that one can obtain from insulin-treated cells a protein kinase B that has been activated *in vivo*, the Alessi et al. reference simply discloses that full activation of protein kinase B requires phosphorylation of Ser473 and Thr308 and the Cross et al. reference simply discloses that protein kinase B phosphorylates GSK3 and thus fail to anticipate or suggest of the currently claimed *in vitro* method for activating protein kinase B.

Claims 1-8 and 22 stand rejected for being allegedly obvious in view of the combined teachings of Wijkander, Alessi, Cross and Vanhaesebroeck (Biochem. J., 2000, 346: 561-576).

Applicant reasserts its arguments above. Vanhaesebroeck merely shows that the addition of PIP3 and PI(3,4)P2 would enhance the activation of PKB. Dependent Claims 5 and 6 recite these two compounds. These claims depend from the currently amended Claim 1, which recites method steps and features (i.e., that the insulin receptor is autophosphorylated, IRS-1 and IRS-2 are phosphorylated, the p85 subunit of PI 3-kinase is bound to IRS-1/-2, and that PI 3-kinase, PDK1, and PDK2 are activated) absent from the combination of Wijkander, Alessi, Cross and Vanhaesebroeck. Even if Vanhaesebroeck teaches the enhancement of the activation of PKB with PIP3 and PI(3,4)P2, it fails to remedy the deficiencies of Wijkander, Alessi, Cross as discussed above since Vanhaesebroeck does not teach an *in vitro* method for activating protein kinase B by reconstituting the entire early insulin signaling pathway.

Claims 1-8 stand rejected for being allegedly obvious in view of the combined teachings of Wijkander, Alessi, Cross and Bauer et al. (General and Comparative Endocrinology, 1983, 49(3):414-427).

Applicant reasserts its arguments above. Bauer merely shows that islet cells from anglerfish contain insulin degrading proteases that are similar to the insulin degrading proteases from rat islet cells. Dependent Claim 7 recites islet cells. Claim 7 depends from Claim 1, which now specifies an *in vitro* method for activating protein kinase B wherein the insulin receptor is autophosphorylated, IRS-1 and IRS-2 are phosphorylated, the p85 subunit of PI 3-kinase is

bound to IRS-1/-2, and PI 3-kinase, PDK1, and PDK2 are activated. Bauer et al. does not remedy the deficiency in Wijkander, Alessi, and Cross as discussed above with respect to Claim 1. It provides only a general teaching of islet cells and does not teach the *in vitro* an *in vitro* method for activating protein kinase B by reconstituting the entire early insulin signaling pathway.

Claims 9-15 stand rejected for being allegedly obvious in view of the combined teachings of Wijkander, Hill and Hemmings (Methods Enzymol., 2002, 345: 448-463), Campbell (Biology, 3rd edition, 1992, Benjamin/Cummings Publishing Co., Inc., page 104), Vanhaesebroeck, Alessi and Cross.

In addressing this rejection, Applicant first notes the amendments to Claim 9 that specify “a plasma membrane fraction which comprises a PDK2 (“phosphoinositide-dependent kinase 2”) activity and a cytoplasmic fraction which comprises a protein kinase B and a PDK1 (“phosphoinositide-dependent kinase 1”) activity”. Applicant further notes the amendments to Claim 9 that specify “producing a desalted aqueous fraction comprising less than 145 mM chloride and said PDK2 (“phosphoinositide-dependent kinase 2”) activity”. As such Claim 9 is directed to a method of activating protein kinase B in vitro where by the PDK1 and PDK2 activities have been resolved into distinct fractions. As discussed on pages 25-26 of the specification (i.e., first paragraph of Example 2), there was considerable uncertainty as to the very existence of a distinct PDK2 activity (i.e., protein kinase B Ser473 phosphorylase) during the time period that preceded filing of the instant application. This is especially important in view of the Examiner’s obligation in rejecting claims under 35USC§103 to avoid hindsight and to cast oneself in the position of one skilled in the art at the time that the invention was made (see MPEP 2141.01 which states: “It is difficult but necessary that the decision maker forget what he or she has been taught ... about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art.” *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).”).

Bearing in mind that the currently amended Claim 9 is directed to a method of activating protein kinase B *in vitro* where by the PDK1 and PDK2 activities have been resolved into distinct fractions, it is evident that the previously considered Wijkander, Vanhaesebroeck, Alessi and Cross references do not teach or suggest this limitation. The Hill and Hemmings reference merely shows an analysis of protein kinase B in subcellular fractions, where the membrane and cytosol fractions may contain protein kinase B. Significantly, the 2002 Hill and Hemmings reference states that “the authentic kinase for Ser-473 is yet to be identified” (Page 448, final sentence of Introduction). Hill and Hemmings thus does not provide any indication that PDK2 (i.e., the “authentic kinase for Ser-473” that “is yet to be identified”) can be resolved into a distinct fraction, let alone a method for accomplishing this. Campbell merely shows that the salt concentration (i.e., the chloride concentration) may affect enzyme function. The combination of the Wijkander, Hill and Hemmings, Campbell, Vanhaesebroeck, Alessi and Cross references fail to teach a method of activating protein kinase B *in vitro* where by the PDK1 and PDK2 activities have been resolved into distinct fractions.

Claims 9-15 also stand rejected for being allegedly obvious in view of the combined teachings of Wijkander, Hill and Hemmings, Campbell, Vanhaesebroeck, Alessi and Cross in view of Bauer et al.

Applicant reasserts its arguments above. Bauer et al. merely shows that islet cells from anglerfish contain insulin degrading proteases that are similar to the insulin degrading proteases from rat islet cells. Dependent Claim 11 recites islet cells. Claim 11 depends from Claim 9, which now specifies an *in vitro* method of activating protein kinase B *in vitro* whereby the PDK1 and PDK2 activities have been resolved into distinct fractions. Bauer et al. does not remedy the deficiency in Wijkander, Hill and Hemmings, Campbell, Vanhaesebroeck, Alessi and Cross as discussed above with respect to the currently amended Claim 9 or dependent Claim 11. Bauer et al. only provides a general teaching of islet cells and does not teach an *in vitro* method for activating protein kinase B whereby the PDK1 and PDK2 activities have been resolved into distinct fractions.

Claims 9-15 stand rejected for being allegedly obvious in view of the combined teachings of Wijkander, Hill et al. (Current Biology., 2002, 12(14): 1251-1255), Campbell, Vanhaesebroeck, Alessi and Cross.

As noted above the currently amended Claim 9 is directed to a method of activating protein kinase B in vitro whereby the PDK1 and PDK2 activities have been resolved into distinct fractions, and it has been established that the previously considered Wijkander, Vanhaesebroeck, Campbell, Alessi and Cross references do not teach or suggest this feature. The Hill et al. reference (Current Biology., 2002, 12(14): 1251-1255) that is dated July 23, 2002 allegedly describes the resolution of PDK2 activity (i.e. PKB Ser-473 kinase activity) into a distinct fraction. However, the Applicants have provided herewith an Affidavit under 37CFR§1.131 and associated Exhibits that demonstrate that the Applicants were in possession of the invention (i.e., a method of activating protein kinase B in vitro where by the PDK1 and PDK2 activities have been resolved into distinct fractions) prior to the July 23, 2002 date of the Hill et al. reference. More specifically, Exhibits 1- 54 show that Provisional U.S. Patent Application No. 60/392,695 was filed by co-inventors Mueckler, Murata, and Hresko, and on June 28, 2002. The instant Non-Provisional Application filed on July 16, 2003 cannot claim priority to Provisional U.S. Application No. 60/392,695 filed on June 28, 2002. However, the records associated with the expired provisional patent application are properly introduced herein under the provisions of 37CFR§1.131 as objective evidence of the Applicants' possession of the claimed invention prior to the July 23, 2002 date of the Hill et al. reference. Exhibit 1 is a copy of the returned postcard indicating that Applicants Mueckler et al. filed a provisional patent application entitled "Cell-Free Assay for Insulin Signaling" comprising a specification of 31 pages, 3 pages of claims and 11 sheets of formal drawings with the United States Patent and Trademark Office (USPTO) on June 28, 2002 as evidenced by the affixed USPTO date stamp sticker with the number "60/392695" and the date 6/28/02. Exhibit 2 is a copy of the reverse side of that postcard. Exhibit 3 is a copy of the Express Mail label for item "EL474179041 US" mailed on June 28, 2002. Exhibit 4 is a copy of the filing fee check dated 6/28/02 and return receipt postcard prior to mailing. Exhibit 5 is the cover sheet for the provisional application that is signed and dated on 6/28/02 and lists the Express Mail label number EL4749041 US. Exhibit 6 is the first page of

the specification filed on June 28, 2002 that lists the Express Mail label number EL4749041 US. Exhibits 6 through 54 comprise the entire specification, claims, drawings and sequence listing of Provisional Patent Application No. 60/392,695. The specification, claims, drawings, and abstract of the instant non-provisional application appear to be identical to the specification, claims, drawings, and abstract of the provisional application, with the exception of the presence of a page 30 (Exhibit 35) in the provisional application. As noted in this response, page 30 was apparently not filed in the instant non-provisional application. Nonetheless, the content of the provisional application filed by the Applicants on June 28, 2002 clearly shows possession of the key elements of Claim 9 related to a method of activating protein kinase B in vitro whereby the PDK1 and PDK2 activities have been resolved into distinct fractions. For example, pages 25 through 29 (Exhibits 30 through 34) and drawings (Exhibits 48, 49, 50), both of the provisional application, show that: i) PDK2 activity (i.e., Ser473 kinase activity) could be separated into a membrane fraction with negligible PDK1 activity (i.e., Thr308 kinase activity), ii) PDK1 activity could be separated into a cytoplasmic fraction with negligible PDK2 activity, iii) PDK2 activity could be displaced from a membrane fraction into an aqueous fraction by salt-extraction, iv) the salt-extracted aqueous fraction could be desalted and added back to an assay mixture comprising the salt-extracted plasma membrane fraction, the cytoplasmic fraction, ATP, and a phosphatidylinositol phosphate molecule in a buffer comprising less than 145 mM chloride, and that, v) the resultant assay mixture would result in activation of protein kinase B (i.e., phosphorylation of both Ser473 and Thr308 of protein kinase B). Further evidence that the Applicants were in possession of the invention as claimed as of June 28, 2002 is at least found in the Summary of the Invention section (Exhibits 13-14), the Description of the Drawings section (Exhibits 17-18), and the Overview of the Invention section (Exhibit 21).

Given that the Declaration made under 37CFR§1.131 and the objective evidence provided by the associated Exhibits clearly establish possession of the claimed invention on June 28, 2002, the Applicants respectfully submit that the Hill et al. reference of July 23, 2002 does not constitute prior art and should be withdrawn. In the absence of the Hill et al. reference, the Wijkander, Campbell, Vanhaesebroeck, Alessi and Cross references neither teach nor suggest a method of activating protein kinase B in vitro whereby the PDK1 and PDK2 activities have been

resolved into distinct fractions. Applicant therefore respectfully requests that the rejections of Claims 9-15 under 35USC§103 in view of the combined teachings of Wijkander, Hill et al., Campbell, Vanhaesebroeck, Alessi and Cross be withdrawn.

Claims 9-15 also stand rejected for being allegedly obvious in view of the combined teachings of Wijkander, Hill et al. (Current Biology., 2002, 12(14): 1251-1255), Campbell, Vanhaesebroeck, Alessi and Cross in view of Bauer et al.

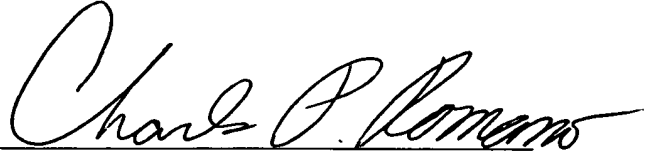
Applicant reasserts its arguments above. Bauer et al. merely shows that islet cells from anglerfish contain insulin degrading proteases that are similar to the insulin degrading proteases from rat islet cells. Dependent Claim 11 recites islet cells. Claim 11 depends from Claim 9, which now specifies an *in vitro* method of activating protein kinase B in vitro whereby the PDK1 and PDK2 activities have been resolved into distinct fractions. Bauer et al. does not remedy the deficiency in Wijkander, Hill et al. (Current Biology., 2002, 12(14): 1251-1255), Campbell, Vanhaesebroeck, Alessi and Cross as discussed above with respect to the currently amended Claim 9 or dependent Claim 11. Bauer et al. only provides a general teaching of islet cells and does not teach an *in vitro* method for activating protein kinase B whereby the PDK1 and PDK2 activities have been resolved into distinct fractions.

CONCLUSION

All of the stated grounds of rejection and objection have been properly traversed, accommodated, or rendered moot. Applicant, therefore, respectfully requests that the Office reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action, and as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, she is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Response is respectfully requested.

Respectfully submitted,

A handwritten signature in cursive script, reading "Charles P. Romano". The signature is written in dark ink and is positioned above a horizontal line.

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Attachments